REMARKS

As a preliminary matter, the undersigned would like to thank the Examiner and his supervisor for taking the time to conduct the telephonic interview on April 10, 2003 with Applicants' representatives to discuss the rejections.

For convenience, the rejections are addressed in the order in which they were presented in November 20, 2002 Office Action. Appendix A shows the pending claims subject to examination.

Status of the claims

Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 are pending and under examination. Applicants would like to direct the Examiner's attention to the response filed November 12, 1999, wherein claims 3 and 10 were cancelled.

First Rejection under 35 U.S.C. § 103

Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 310-329, 331-337, and 347-356 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Grinstaff (U.S. Patent No. 5,498,421) in view of Wallach (U.S. Patent No. 4,853,228), Allen (U.S. Patent No. 5,620,689), and Ginsberg (U.S. Patent No. 5,656,442).

According to the Action, Grinstaff teaches a composition for the delivery of diagnostic or therapeutic agents that meets the limitations of the vesicles claimed in the present application. In particular, it is asserted that the polymeric shell that encases the biologic as described in Grinstaff may be modified to include a phospholipid and may be conjugated to a targeting

moiety. The Action cites the Wallach, Allen, and Ginsberg references in combination with Grinstaff to demonstrate that covalent linkages between lipid vesicles and targeting ligands such as RGD are known in the art. In response to Applicant's previously filed argument that the Grinstaff compositions are different from those claimed in the present application at least because they are not substantially free of crosslinked proteins and polymers, it is stated that nowhere in the Grinstaff teaching is the polymeric shell limited to more than 50% crosslinking. Applicants respectfully traverse.

The Grinstaff patent explicitly states that the polymeric shells are "substantially crosslinked" (column 8, lines 11 to 13). The same language is employed in the claims of Grinstaff, which state "wherein said polymeric shell comprises a biocompatible material which is ***substantially crosslinked*** by way of disulfide bonds." See Claim 1. Throughout the Grinstaff specification, the importance of crosslinking in the polymeric structure is emphasized. For example, in column 20, lines 12-39, hemoglobin compositions as disclosed and claimed by Grinstaff are compared to encapsulated hemoglobin compositions of the prior art that are said to leak soluble hemoglobin. The Grinstaff compositions are said to be insoluble due to their **extensively crosslinked** nature (column 20, lines 20 to 22). The Grinstaff constructs are also said to avoid toxicity associated with the soluble hemoglobin compositions of the prior art due to their **extensively crosslinked** nature (column 20, lines 31 to 33).

It is well settled in the courts that words in a claim are presumptively given their ordinary meaning as they would be understood by one of ordinary skill at the time of invention unless it is "expressly" and "specifically stated" in the specification or the prosecution history that the patentee intended to use the words differently. *See, e.g., Digital Biometrics Inc., v. Indentix, Inc.,* 149 F.3d 1335, 1344 (Fed. Cir. 1998). Non-technical terms should be given their ordinary

meaning unless intrinsic evidence indicates otherwise; "technical terms" should be given the meaning they would be given by persons of ordinary skill in the art. *Vitronics*, 90 F.3d at 1582 (quoting *Hoechst Celanese Corp. v. BP Chem. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996)). Dictionaries, encyclopedias, and treatises are particularly useful for determining the ordinary and customary meanings of claim terms. *See, e.g., Texas Digital Systems, Inc., v. Telegenix, Inc.*, 308 F.3d 1193, (Fed. Cir. 2002); *Amgen Inc., v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). Furthermore, according to the MPEP, while a term in the claims may be given a special meaning in the description of the invention, generally no term may be given a meaning repugnant to the usual meaning of the term. *In re Hill,* 161 F.2d 367, 73 USPQ 482 (CCPA 1947). MPEP 2173.05(b).

Despite the use of the terms "extensively crosslinked" and "substantially crosslinked" in the Grinstaff description and claims, nowhere in the Grinstaff specification are the terms defined. The MPEP and recent Federal Circuit Court decisions require, therefore, that the terms "substantially" and "extensively" as used in the Grinstaff patent be given their ordinary and usual meaning. In the Merriam-Webster's Collegiate Dictionary, 12th Edition, the term "substantial" is defined as "being largely but not wholly that which is specified." The term "extensively" is defined as "having wide or considerable extent". Although neither of those dictionary definitions provide numbers or percentages, Applicants submit that an entity that is "largely but not wholly crosslinked" is, by definition, greater than 50% crosslinked. Accordingly, the present claims distinguish over Grinstaff as the presently claimed vesicles are ***less than*** 50% crosslinked. Accordingly, a combination of the Grinstaff, Wallach , Allen, and Ginsberg references cannot render the instant claims obvious. There is simply no motivation or suggestion provided in any of the cited references to prepare targeted gas-filled vesicles which comprise one or more

membranes encapsulating an inner void wherein the membranes are substantially free of crosslinked proteins and polymers. In fact, Grinstaff *teaches away* from such a vesicle by emphasizing the necessity and desirability of substantially crosslinked polymeric shells. Accordingly, Applicants respectfully request that the rejection of claim 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 310-329, 331-337, and 347-356 under 35 U.S.C. § 103(a) as allegedly unpatentable over Grinstaff (U.S. Patent No. 5,498,421) in view of Wallach (U.S. Patent No. 4,853,228), Allen (U.S. Patent No. 5,620,689), and Ginsberg (U.S. Patent No. 5,656,442) be withdrawn.

Second Rejection under 35 U.S.C. § 103

Claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 310-329, 331-337, and 347-356 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wallach (U.S. Patent No. 4,853,228) and Allen (U.S. Patent No. 5,620,689) in view of Schneider (U.S. Patent No. 5,643,553), Porter (U.S. Patent No. 5,648,098) and Ginsberg (U.S. Patent No. 5,656,442).

According to the Action, it would have been obvious to one of ordinary skill in the art to employ gaseous moieties, as taught by Schneider and Porter, with the liposomes of Wallach and Allan because, as suggested by Schneider and Porter, the ordinary artisan would have expected to enhance the drug delivery of the agent of choice using gaseous vesicles that are attached to a suitable targeting agent, such as those taught by Ginsberg. In response, Applicants respectfully traverse.

As explained in the MPEP, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify

the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in Applicants disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants assert that a *prima facie* case of obviousness has not been established at least because there is no suggestion or motivation to modify the references.

There is no Suggestion or Motivation to Modify the References

Applicants submit that there is no evidence of record indicating that those of ordinary skill would have been motivated to combine the teachings of the cited references in the manner that the Action proposes, much less that such a combination would have produced the claimed invention.

The present claims are directed to a targeted gas-filled vesicle which comprises one or more membranes encapsulating an internal void. In contrast, the Schneider patent is directed to compositions comprising microbubbles of air or physiologically acceptable gases. It is apparent from the text of the Schneider patent that, despite the Action's assertion otherwise, Schneider's microbubble containing compositions are unlike the vesicles claimed in the present application. For example, Schneider defines the term "microbubble" as follows:

> In this disclosure, the term of "microbubble" specifically designates air or gas globules in suspension in a liquid which generally results from the introduction therein of air or gas in divided form, the liquid preferably also containing surfactants or tensides to control the surface properties thereof and the stability of the bubbles. More specifically, one may consider that the internal

> volume of the microbubbles is limited by the gas/liquid interface, or in other words, the microbubbles are only bounded by a rather evanescent envelope involving the molecules of the liquid and surfactant loosely bound at the gas to liquid junction boundary.

See Schneider, column 1, lines 27 to 38. The Schneider "microbubbles" are then compared to "microcapsules" or "microballoons:"

> In contrast, the term of "microcapsule" or "microballoon" designates preferably air or gas bodies with a material boundary or envelope formed of molecules other than that of the liquid of suspension, e.g., a polymer membrane wall.

See Schneider, column 1, lines 39 to 42. In an effort to distinguish the Schneider evanescently enveloped microbubbles from prior art microcapsules and/or microballoons, the following is stated:

> It is important to note that no confusion should be made between the present invention and the disclosure of Ryan (U.S. Pat. No. 4,900,540) reporting the use of air or gas filled liposomes for echography. In this method Ryan encapsulates air or a gas within liposomic vesicles; in embodiments of the present invention microbubbles of air or a gas are formed in suspension of liposomes (i.e. liquid filled liposomes) and the liposomes apparently stabilize the microbubbles. In Ryan, the air is inside the liposomes, which means that within the bounds of the presently used terminology, the air filled liposomes of Ryan belong to the class of microballoons and not to that of the microbubbles of the present invention.

See Schneider, column 4, lines 14 to 26. From the text quoted above, Applicants submit respectfully that it is abundantly clear that Schneider is *not* directed to vesicles containing a gas or gaseous precursor as described and claimed in the present application[1]. Instead, Schneider is

[1] During prosecution of U.S. Patent No. 5,271,928, the parent application to U.S. Application No. 5,643,553, Schneider's representatives clearly describe the Schneider compositions as having no encapsulated structures, "in the compositions of the present invention, the microbubbles of air or gas formed as a suspension within the aqueous carrier phase and are stabilized in that phase by the presence of the surfactant(s). There is no encapsulated structure in the presently claimed compositions." U.S. Patent Nos. 5,271,928 and No. 5,643,553 share the same specification. Response filed April 8, 1993, enclosed for Examiner's convenience as Exhibit A.

clearly directed to compositions containing divided globules of gas which are stabilized by components of the aqueous media. Indeed, as indicted by the quote above, to the extent that Schneider teaches liposomes, they are filled with *liquid*.

It is submitted respectfully that the text which is set forth in the Schneider patent and which is reproduced above was not fully considered in the Action. When such text is considered, it is abundantly clear that the gas and gaseous precursor filled vesicles of Applicants' invention are neither disclosed nor suggested by Schneider. Accordingly, the Schneider reference cannot be said to teach, motivate, or suggest the gas filled compositions of the present invention. As the case law mandates, "[i]t is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Furthermore, because the Action points to nothing in the Wallach, Allen, Porter or Ginsberg references that supplies the missing teaching, *i.e.*, the possibility or desirability of targeted gas-filled vesicles which comprise one or more membranes encapsulating an internal void, the combination of cited references cannot be said to motivate or suggest the vesicles claimed in the present application. The Action provides no showing as to what in the cited references would motivate one of skill to construct a gas-filled vesicle as recited in claim 1. Accordingly, Applicants respectfully request that the rejection of claims 100, 102, 103, 127, 194-200, 203, 210-228, 294-300, 310-329, 331-337, and 347-356 under 35 U.S.C. § 103(a) as allegedly unpatentable over Wallach (U.S. Patent No. 4,853,228) and Allen (U.S. Patent No. 5,620,689) in view of Schneider (U.S. Patent No. 5,643,553), Porter (U.S. Patent No. 5,648,098) and Ginsberg (U.S. Patent No. 5,656,442) be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicant submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

Date: April 21, 2003

Leslie E. Aberman
Limited Recognition Under 37 CFR§ 10.9(b) attached

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EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

SCHNEIDER et al

Atty. Ref: 1201-3

Serial No. 07/775,989

Group: 1209

Filed: 20 November 1991

Examiner: Russell

For: STABLE MICROBUBBLES SUSPENSIONS INJECTABLE INTO LIVING ORGANISMS

* * * * * * * * * * * * * * * * *

April 8, 1993

93 APR 13 AM 12:18

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

R E S P O N S E

Sir:

In response to the official action mailed January 15, 1993, please amend the above-identified application as follows:

IN THE SPECIFICATION

Page 5 lines 23-24, delete ", as defined in claim 1,"

Page 6 line 20, delete "or air" and replace by --of air--

IN THE CLAIMS:

Please cancel claims 19 through 23 and 26-27 without prejudice.

Please cancel claims 1-18 and replace by the following new claims.

28. A composition suitable for injection into the bloodstream and body cavities of living beings, comprising a suspension of stabilized air or gas microbubbles in a physiologically acceptable aqueous carrier phase having from about 0.01 to about 20% by weight of one or more dissolved or dispersed surfactants, at least one of said surfactants being a film forming surfactant present in the composition at least partially in lamellar or laminar form.

29. The composition of claim 1, wherein the lamellar surfactant is in the form of mono- or pluri-molecular membrane layers.

30. The composition of claim 28, containing about 10^8 - 10^9 bubbles of 0.5 - 10μm size/ml.

31. The composition of claim 28, wherein the surfactant is a phospholipid.

32. The composition of claim 31, wherein said phospholipid is selected from the group consisting of lecithins, phosphatidic acid, phosphatidyl-choline, phosphatidyl- ethanolamine, phosphatidyl-serine, phosphatidyl-glycerol, phosphatidyl-inositol, cariolipin and sphyngomyelin.

33. The composition of claim 31, and further comprising a substance affecting the properties of liposomes selected from the group consisting of phosphatidyl-glycerol, dicetyl-phosphate, cholesterol, ergosterol, phytosterol, sitosterol, lanosterol, tocopterol, propyl gallate, ascorbyl palmitate and butylated hydroxy-toluene.

34. The composition of claim 28, and further comprising a dissolved viscosity enhancer or stabilizer selected from the group consisting of linear and cross-linked poly- and oligo-saccharides, sugars, hydrophilic polymers and iodinated compounds in a weight ratio to the surfactants of between about 1:5 to 100:1.

35. The composition of claim 34, wherein said iodinated compound is Iopamidol.

36. The composition of claim 28, wherein the surfactants comprise up to 50% by weight of non-laminar surfactants selected from the group consisting of fatty acids, esters and ethers of fatty acids and alcohols with polyols.

37. The composition of claim 36, wherein the non-laminar surfactant is selected from the group consisting of polyalkylene glycols, polyalkylenated sugars and polyalkylenated glycerol.

38. A method for the preparation of a composition as defined in claim 28, said method comprising the steps of:

(a) selecting at least one film forming surfactant and converting it into lamellar form;

(b) contacting the surfactant in lamellar form with air or an adsorbable or entrappable gas for a time sufficient for that air or gas to become bound by said surfactant; and

(c) admixing the surfactant in lamellar form with an aqueous liquid carrier, to form a stable dispersion of air or gas microbubbles in said liquid carrier.

12 ~~39~~. The method of claim 11 ~~38~~, wherein step (c) is performed before step (b), step (b) being effected by introducing pressurized air or gas into the liquid carrier and thereafter releasing the pressure.

13 ~~40~~. The method of claim 11 ~~38~~, wherein step (c) is brought about by gentle mixing of the components with no shaking, whereby air or gas bound to the lamellar surfactant in step (b) develops into a suspension of stable microbubbles.

14 ~~41~~. The method of claims 11 ~~38~~, wherein the aqueous liquid carrier contains dissolved therein stabilizer compounds selected from the group consisting of hydrosoluble proteins, polypeptides, sugars, poly- and oligo-saccharides and hydrophilic polymers.

15 ~~42~~. The method of claim 11 ~~38~~, wherein step (a) is effected by coating the surfactant onto particles of soluble or insoluble materials, wherein step (b) is effected by letting the coated particles stand for a while under air or gas and step (c) is effected by admixing the coated particles with an aqueous liquid carrier.

16 ~~43~~. The method of claim 11 ~~38~~, wherein step (a) is effected by sonicating or homogenizing under high pressure an aqueous solution of film forming lipids, leading, at least partly, to the formation of liposomes.

17 ~~44~~. The method of claim 16 ~~43~~, wherein step (b) is effected by freeze-drying the liposome containing solution and contacting the resulting freeze-dried product with air or a gas.

~~45~~ 18. The method of claim ~~44~~ 17, wherein in step (b) the liposome containing solution contains hydrophilic stabilizers.

~~46~~ 19. The method of claim ~~43~~ 16, wherein the aqueous solution of film forming lipids also contains viscosity enhancers or stabilizers selected from the group consisting of hydrophilic polymers and carbohydrates in weight ratio relative to the lipids of between 1:5 and 100:1.

END

REMARKS

Reconsideration of this application is requested.

At the outset, the undersigned wishes to thank the Examiner (Mr. Russell) for kindly agreeing to conducting an interview on this application. The interview was held on April 6, 1993, and the courtesies extended by the Examiner were most appreciated.

With reference to the restriction requirement discussed on page 2 of the action, the election of Group I, namely claims 1-18, is hereby affirmed. Claims 19-23 and 26-27 have been cancelled without prejudice to pursuing that subject matter in one or more divisional applications.

The specification has been objected to, and claims 1-18 rejected, under 35 USC 112, first paragraph, as failing to provide an enabling disclosure on the ground that air is known to cause emboli which may result in death. The Examiner has concluded that the disclosure does not adequately teach how to make or use the invention. That rejection is traversed for the following reasons.

This point was discussed during the interview. It was noted that the applicants have been actively involved in all aspects of products related to those of the present invention for several years and are unaware of any alleged hazards. During the development of the technology, several thousand injections of air or gas microbubble suspensions have been made into dozens of experimental animals, including rabbits, pigs, rats and monkeys. Several of those animals have had several dozens of injections

without manifesting the slightest indication of emboli. No hazards are believed to arise with respect to the use of the composition of the present invention. Certainly, compositions which would give rise to health hazards when administered are not encompassed by the present invention. Reconsideration and withdrawal of the rejection is accordingly requested. If the Examiner decides to pursue this rejection, it is requested that the applicants be provided with tangible information, such as a patent or a literature reference, which serves to support the Examiner's position.

With reference to the how-to-make and how-to-use disclosure, it is believed that the specification clearly contains a fully enabling disclosure. The description beginning at page 7 describes how to make the compositions of the invention, and the use of the compositions is described beginning at page 14, and in the working examples. Reconsideration and withdrawal of this particular formal rejection is accordingly respectfully requested.

Claims 1-18 have been rejected on formal and prior art grounds for the reasons set forth on pages 3-7 of the action. In response to those rejections, claims 1-18 have been cancelled and replaced by new claims 28-46. For the reasons discussed below, it is believed that the new claims presented with this response obviate the outstanding formal points, and also define subject matter which is clearly patentably distinguished from

the cited teachings. Withdrawal of all of the outstanding rejections is accordingly respectfully requested.

Claims 1-18 have been rejected under 35 USC 112, second paragraph, for the reasons set forth on pages 3-4 of the action. The points raised by the Examiner have received attention in the preparation of the new claims. Thus, the new claims do not employ language such as "e.g.", "characterized in that", "one or more", "such as" and "affecting the properties of". Moreover, proper Markush language has been used where appropriate.

The Examiner has objected to the terms "at least", "one or more" and "at least partially". These expressions were specifically discussed with the Examiner. It is the applicants' position that no uncertainty arises with respect to those terms. "At least one" and "one or more" mean exactly what they say, namely one or more than one. "At least partially" means partially or more than partially, i.e. up and including completely. It is believed that the meaning of these terms is clear and that they would be readily understood by a person of ordinary skill. They have accordingly been used in new claim 28. Reconsideration of this aspect of the formal rejection is accordingly respectfully requested.

New claim 28 is based on previous claim 1, and new claims 29-42 are based on previous claims 2 and 6-18. New claim 28 also specifies that the suspension is stabilized by the presence of the surfactants. Basis for that appears at page 7 lines 1-2 of the application as originally filed.

In light of the above, it is believed that the outstanding formal rejection of the claims has been obviated. Withdrawal of that rejection is accordingly respectfully requested.

Claims 1-6 have been rejected under 35 USC 102(b) as being anticipated by U.S. patent 4,900,540 to Ryan et al (hereinafter Ryan). That rejection is traversed for the following reasons.

As explained during the interview, the present invention is directed to a composition suitable for injection into the bloodstream and body cavities of living beings. The composition comprises the suspension of stabilized air or gas microbubbles in a physiologically acceptable aqueous carrier phase having from about 0.1 to about 20% by weight of one or more dissolved or dispersed surfactants. At least one of the surfactants is a film-forming surfactant present in the composition at least partially in lamellar or laminar form.

It is important to note that the composition as now claimed in claim 28 is defined as comprising a suspension of stabilized air or gas microbubbles in the physiologically acceptable aqueous carrier phase. Basis for the suspension feature appears at page 6 line 20 of the application as originally filed.

The distinctions between the Ryan teaching and the compositions of the present invention were discussed in detail during the interview. Thus, it was pointed out that Ryan describes air or gas filled liposomes(sometimes referred to as

"microballoons") suitable for administration to a patient to permit organ imaging using ultrasound techniques.

The present invention is not concerned with microballoons. Rather, the presently claimed composition comprises a suspension of stabilized air or gas microbubbles contained in a physiologically acceptable aqueous carrier phase. These air or gas microbubbles are not bounded by a tangible material envelope such as a membrane, as are the Ryan microballoons, but instead are present in the aqueous carrier phase as a suspension microbubbles with no tangible outer envelope. Put more simply, the "envelope" for the microbubbles present in the suspensions of the present invention is the gas/liquid interface itself. In this way, the air or gas is confined as a microsphere by the surface forces of the liquid carrier itself. These forces are influenced by the presence of surfactants in the liquid, which permits the total size and number of microbubbles present in the suspension to be controlled according to the desired end use.

The present invention is concerned only with suspensions of microbubbles, and does not relate to microballoons or gas-filled vesicles, such as those described by Ryan. This is, in fact, already discussed in the application as originally filed in the first complete paragraph appearing on page 6. As noted there, the air is encapsulated within the liposomes whereas, in the compositions of the present invention, the microbubbles of air or gas are formed as a suspension within the aqueous carrier

phase and are stabilized in that phase by the presence of the surfactant(s). There is no encapsulated structure in the presently claimed compositions.

Ryan clearly does not anticipate the presently claimed compositions. The structures of the two materials are entirely different. Withdrawal of the anticipation rejection based on Ryan is accordingly respectfully requested.

Claims 1-7 have been rejected under 35 USC 102(e) as anticipated by U.S. patent 5,088,499 to Unger. That rejection is traversed for the following reasons.

It is noted, at the outset, that the filing date of the Unger patent was August 20, 1990 which is subsequent to the April 2, 1990 priority date of the present application. However, it is noted that Unger is a continuation-in-part of application serial number 455,707, filed December 22, 1989. The disclosure of serial number 455,707 has not been studied, and so it is unclear whether the teaching of that application is pertinent to the presently claimed invention. The applicants reserve the right, should the rejection based on Unger be pursued by the Examiner, to review the teaching of serial number 455,707. For the reasons discussed below, it is believed that Unger, at least as far as the disclosure contained in the issued patent is concerned, does not anticipate or render obvious the presently claimed compositions.

Unger, like Ryan, relates to liposomes having an encapsulated gas therein (see the Abstract). Unger therefore

relates to "microballoon" technology, and not to suspensions of microbubbles as claimed in the present invention. Unger therefore does not anticipate the presently claimed compositions. Withdrawal of the outstanding rejection based on Unger is accordingly respectfully requested.

Claims 1-10 have been rejected under 35 USC 103 as being unpatentable over the combined teachings of Ryan and Unger when taken in view of European patent 131,540 to Rasor, U.S. patent 4,466,442 to Hillmann et al and WO/09165 to Schneider et al. That rejection is traversed for the following reasons.

The deficiencies of Ryan and Unger have been discussed above. Neither of those references teaches or suggests suspensions of microbubbles as claimed in the present application. Both of those references are directed to air or gas-filled microspheres (i.e. "microballoon" technology) and are therefore unrelated to the presently claimed invention.

The deficiencies of Ryan and Unger are certainly not cured by the secondary references relied on by the Examiner. As noted on page 5 of the action, the secondary references are relied on for their teaching that other surfactants are known in the art to be useful in preparing ultrasound agents. Examples of the various teachings of those references are given by the Examiner in the last two sentences appearing on page 5 of the action. Other than the fact that the secondary references teach that other surfactants may be useful, the secondary references are irrelevant so far as the presently claimed invention is

concerned. Certainly, there would have been no motivation to a person of ordinary skill to modify the basic teachings of Ryan and Unger on the basis of the secondary references. Absent any such motivation to modify those teachings to arrive at suspensions of microbubbles, it is clear that the references relied on by the Examiner cannot be give rise to a prima facie case of obviousness against the presently claimed invention. Withdrawal of the obviousness rejection is accordingly respectfully requested.

Claims 11-18 have been rejected under 35 USC 103 as being unpatentable over the combined teachings of Unger, Ryan and Hillmann et al when taken in view of U.S. patent 4,229,360 to Schneider. The latter reference is relied upon for its teaching that liposomes may be freeze-dried.

As with the obviousness rejection discussed above, the obviousness rejection of claims 11-18 is unsound in as much as it relies on Unger and Ryan which are irrelevant for the reasons discussed above. Schneider does not cure the deficiencies of those references. Withdrawal of this obviousness rejection is accordingly respectfully requested.

During review of the specification, one or two grammatical and typographical errors have been noted. Those have been corrected in the present response. No new matter has been entered.

In the circumstances, it is believed that this application is now in a form suitable for immediate allowance. Early action to that effect is requested.

Respectfully submitted,

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